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ORIENTAL SORE.

SECOND REVIEW OF SOME OF THE RECENT
ADVANCES IN TROPICAL MEDICINE.

A.Balfour and R.G.Archibald.

1911.



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ORIENTAL
SORE.

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SECOND REVIEW

OF SOME OF THE

RECENT ADVANCES IN TROPICAL MEDICINE

HYGIENE AND TROPICAL VETERINARY SCIENCE

BEING A SUPPLEMENT TO THE

FOURTH REPORT

OF THE

WELLCOME TROPICAL RESEARCH LABORATORIES

AT THE

GORDON MEMORIAL COLLEGE

KHARTOUM

BY

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KHARTOUM

BY

BAILLIÈRE, TINDALL & COX

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Ophthalmia—conjunctivitis*almost the only organisms occurring are the Koch-Weeks' bacillus, perhaps, also, the influenza bacillus and the pneumococcus (in Egypt the gonococcus also, rarely *B. subtilis*). MacCallan, whom he also quotes, says that acute ophthalmias in Egypt are more liable to transmission by flies than is trachoma. The spread of the latter is mainly effected by direct contact of the fingers, clothes, etc.

continued

Articles on the "trachoma" bodies of Halberstädter and v. Prowazek will be found in the *Medical Annual* for 1910 and 1911, where there is a great deal also about the treatment of conjunctivitis. Whatever the nature and significance of these bodies, and they appear to belong to the Chlamydozoa, it has not been proved that they occur in other conditions besides trachoma. Working in Manila, Edwards¹ has isolated from trachoma cases a small organism to which he has given the name of *B. trachus*, but, as he himself admits, there is no evidence that it is a cause of trachoma.

Oriental Sore. This is a bad name for the condition we are about to discuss. Perhaps it had better be termed "Cutaneous Leishmaniasis," and yet this again would appear to be scarcely correct, as quite recently the condition has been found affecting the buccal mucous membranes. Perhaps "Superficial Leishmaniasis" would serve, but, however that may be, fresh interest has been evinced in the subject, doubtless in part from Manson's pronouncements and suggestions regarding it, and still more from the discovery of infantile Leishmaniasis, the success which has attended cultural methods, and the ever-growing enthusiasm for working out the problems presented by tropical medicine. Most of the papers for review deal each with so many aspects of the condition that it is not easy to group them, but those dealing specially with treatment will be taken last.

A general paper is that by Marzinowsky² which, however, is now somewhat out of date, and contains nothing very special except possibly some therapeutic notes, which will be mentioned in due course, and the observation that he succeeded in infecting himself by employing a special technique.

Nattan-Larrier and Bussière³ have studied *L. tropica*, finding the parasite best stained in sections by means of Unna's polychrome blue, followed by differentiation with oil of cloves. The stain should act for half-an-hour. Carbol thionin also gave good results. Careful preliminary fixation is required. The majority of the parasites are contained in the large macrophages. A great number are found in the connective tissue cells, but none in the plasma cells. The endothelium of blood capillaries may harbour them, but none were seen in the lumina of blood-vessels. Some, however, were observed floating in the cavity of the lymphatics. They find the *Leishmania* most abundant in the spreading part of the sore, and therefore in its depths and at its periphery. Free forms, besides occurring in the lymphatics, may be found in the connective tissue spaces, and even on the surface of the lesion. Important work has been carried out in the Pasteur Institute at Tunis, and perhaps it will be best to take all the papers describing it together.

Nicolle and Sicre⁴ describe the parasite, and note its absence from the peripheral blood. They found an increase of the mononuclear elements at the expense of the polymorphs. Culture on blood-salt-agar, and also on Novy-MacNeal, was successful, and the flagellated culture forms are described. They were grown at a temperature of between 19° and 23° C. Subcultures were easy, and at a temperature of 22° C. vitality was maintained for two months. The cultural forms differ from those of kala-azar. There is an early division of the flagellum in *L. tropica*, and it is longer and more flexible than in *L. donovani*. The authors record that a

monkey (*Macacus sinicus*) inoculated with the virus of the disease on the upper lids and on the root of the nose in the skin, and on both sides of the forehead by scarification, developed highly characteristic lesions in the two first situations, but only a very small and transient papule on the forehead. The primary lesions lasted twenty-one days, and smears taken from them showed the undoubted presence of *Leishmania*. One out of two *M. sinicus* inoculated under the same conditions as the first, with second cultures eighteen days old, developed, after an incubation of thirty-eight days, a nodule which persisted for thirty days, when it was excised. Smears taken from it showed parasites, generally much altered, within the mononuclears and extra-cellular bodies of quite normal appearance.

¹ Edwards, R. T. (1910), "Conjunctival Infection in Manila." *American Society of Tropical Medicine. Collected Papers.*

² Marzinowsky, E. J. (December 28, 1908), "Die Orientbeulen und ihre Ätiologie." *Zeit. f. Hyg. u. Infekt., Vol. LVIII.*

³ Nattan-Larrier, L., and Bussière, A. (January 13, 1909), "Répartition des *Leishmania* dans le Bouton d'Orient." *Bull. Soc. Path. Exot.*

⁴ Nicolle, C., and Sicre, A. (1908), "Recherches sur le Bouton d'Orient." *Arch. de l'Inst. Past., Tunis, No. III.*

Experimenting further with another species of monkey, these observers¹ found that cultures of *L. tropica* exhibited but a feeble virulence. They failed with intradermic, corneal, and ocular inoculations on the dog, cat, and rabbit (see also page 222). Row² was one of the first to cultivate *L. tropica* successfully, using serum cultures. He did so in Bombay, and concludes a well-illustrated and interesting paper as follows :—

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(1) The parasite of the Oriental sore when full developed into the flagellate form, under ordinary conditions of culture, is much longer and bigger than that of kala-azar, in which one meets with short and fat forms as a rule.

(2) The parasite of the Oriental sore is more resistant to external conditions than that of kala-azar—in other words it is much less delicate, as it is found possible to obtain developmental forms up to the flagellates from this parasite (of the Oriental sore) three days after the parasites are removed from the lesion—while the parasite of kala-azar, according to Rogers, dies within twenty-four hours after it leaves the spleen, if it is not cultured within that period.

(3) The flagellum of the parasite of the Oriental sore is much longer, and presents more regular wavy undulations than that of kala-azar, where it is shorter, and where the undulations, if any, are not regular or uniform.

(4) Although contamination of the material with extraneous germs is inhibitory to the early developmental progress of the parasite of the Oriental sore, it is not so destructive to its further development into flagellates as in the case of the parasite of kala-azar where, according to Rogers, even the slightest contamination with staphylococci is sufficient to destroy the culture.

(5) The parasite of the Oriental sore develops into fully mature flagellate forms between forty-eight and seventy-two hours, while that of kala-azar takes twice as long, if not longer.

(6) The best culture medium (according to my results) for the parasite of the Oriental sore is human blood serum, by preference that from tuberculous patients, while that for the parasite of kala-azar is, according to Rogers, sodium citrate 2 to 8 in sodium chloride 0 to 8 solution mixed up with splenic puncture blood.

(7) The optimum temperature for the growth of the parasite of the Oriental sore is between 25° and 28° C., or even up to 30° C., while for that of kala-azar, it is 22° C., or even less (according to Rogers).

Marzinowsky³ has also succeeded in cultivating the parasite, and as he found Nicolle's special medium the best, its composition and method of preparation may perhaps be given. It has been found very useful in these laboratories and consists of agar 14 grammes, sea-salt 6 grammes, water 900 c.c. This mixture is tubed and sterilised in the autoclave. Defibrinated rabbit's blood is then added in the proportion of 2 of agar to 1 of blood. The tubes are placed for twelve hours in the incubator in an inclined position. Before use they are kept for some days at laboratory temperature to ensure their sterility. The original agar should have a feeble alkaline reaction. After complete neutralisation with litmus, 7 c.c. of a normal solution of soda are added to the litre. The author also used human blood to which 10 per cent. citrate of soda solution had been added. Like other observers he points out the absence of any undulating membrane in the otherwise trypanosome-like culture forms. He gives a schematic drawing showing the supposed cycle of the parasite in the human being, i.e. multiplication by binary division of the nucleus and blepharoplast, and the cycle found in culture forms, and, presumably, also in the insect vector. He shows male and female forms, and illustrates conjugation, but it is doubtful if this is a correct interpretation of the phenomena he has observed. Markham Carter⁴ has added considerably to our knowledge of the condition as met with in India, and holds somewhat different views to other observers. In his first paper he says :—

In the light of the experiments described below, it is certain, in the first place, that true Oriental sore is due to a localised cutaneous infection by one or more species of protozoan which can under suitable conditions in culture develop from the early inert torpedo or cockle-shaped forms found in the infected tissues to the fully-developed monadine flagellated organism crithidial in type.

In the second place, it is certain that the view held by Manson and other workers, that the parasite of Oriental sore represents a localised infection by *Leishmania donovani*, whereas kala-azar is a generalised infection of the body with the same parasite, is entirely wrong. The parasite, though morphologically somewhat similar in the early form of Oriental sore, differs from *Leishmania* as much in culture as it does in the manner it attacks man, in that the parasites develop to their final stage of flagellated organisms in symbiotic relationship with cocci and bacteria. Further, it is interesting to note that two forms of the parasite occur in culture, the one a blue-staining flagellated organism, the monadine form, representing, in my opinion, the motile sexual form, possibly the male element; the other a red-staining flagellated organism entirely different, possibly the female element. The fact that these two latter forms are found frequently in pairs is highly suggestive of sexual interchange of elements

¹ Nicolle, C., and Siore, A. (1908), "Faible Virulence des Cultures de *Leishmania tropica* pour le Singe" (bonnet chinois). *Arch. de l'Inst. Past., Tunis*, No. IV.

² Row, R. (1909), "Observations on the Development of Flagellated Organisms from the Parasite of Oriental Sore." *Transactions Bombay Medical Congress*.

³ Marzinowsky, E. J. (December 8, 1909), "Cultures de *Leishmania tropica* (s. *Ovoplasma orientale*, s. *Helcosoma tropicum*) parasite du Bouton d'Orient." *Bull. Soc. Path. Exot.*

⁴ Carter, R. M. (September 11, 1909), "Oriental Sore of Northern India a Protozoal Infection." Preliminary Note. *British Medical Journal*.

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previous to the gregariniform phase. The third type found in culture are minute coccoid-like protozoa, the resistant gregariniform phase, or the earliest form of the parasite from which the common types found in the Oriental sore arise.

He then passes on to a discussion on *Leishmania*, *Leptomonas*, *Herpetomonas*, and *Crithidia*, in the course of which he says:—

Both herpetomonas and crithidia are genera whose distinction is based upon the size and shape of the monadine form, and show in general an alternation of monadine flagellate, with gregariniform resting or non-flagellate phases. In the latter the parasites are seen as small rounded pear-shaped or oblong bodies, attached in great numbers to epithelial cells, etc.

The parasites present in this stage two chromatic elements; a nucleus with its intranuclear centrosome lie close to each other at the base of the cell. In some species a trace of the flagellum attached to the extranuclear centrosome is seen.

and he notes that both the fully developed monadine and the gregariniform phases were present in his cultural forms. He then passes to methods of cultivation, the differentiation between kala-azar and Oriental sore, and other matters of such interest and importance that we feel justified in transcribing the greater portion of the notes.

As a result of experimenting with a series of over fifty different blood media at different temperatures, the medium that was found to exactly meet the requirements of the protozoal parasite was made as follows:—

To 29 c.cm. of sterilised citrate solution 10 per cent. add about 3 c.cm. of fluid expressed from the edge of the sore, which contains myriads of the tiny torpedo-shaped and cockle-shaped parasites typical of the disease.

It is advisable to bore through the rosy margin of the sore to a depth of about 1/4 in., or 1/4 in. towards the centre of the infected area, with a short, fairly fine glass pipette, whose tip has been broken off. Smart pressure will give a steady flow of infected blood and serum.

This infected mixture should now be covered, ringed with vaseline, and placed on ice until the remainder of the medium is made up. Take 50 c.cm. of normal human venous blood and allow to stand in an ice-chest for an hour. At the end of this time break up the clot with a fine glass rod and stir until the whole mass is finely broken up. Pour the fluid portion of the blood and serum into sterilised centrifugal tubes, seal with waxed corks, and centrifugalise until large columns of clear serum are obtained. Place these tubes of blood in an incubator, and keep them at 56° C. for five minutes, then allow to cool to 28° C., or laboratory temperature.

Make a series of fifteen pipettes for cultures as follows: Blow a large glass bulb in the centre of a 3 1/2-in. piece of ordinary glass rod, then make a long, narrow drawn-out area above it, twist this whilst soft so as to make a circular tube of narrow calibre above the bulb. Flame the tube until very soft below the bulb, and draw out until a long, thick capillary tube, 7 in., is made. Cut and seal this capillary tube. Plug the short upper end of the tube above the circular tube with wool, and sterilise in hot air.

Following the usual laboratory methods, make a mark on the capillary tube about 1/2-in. from the bulb. Take the volume of the tube from this point to the other end as one unit, and draw fluid up in the bulb with a large rubber teat on the plugged end of the tube. To four units of clear non-activated serum add four units of red blood cells collected below the fine white cell buffy layer. To this add three units of sterilised citrate 10 per cent., and mix the constituents freely in the bulb by shaking. To the mixture add four units of infected citrate taken from the sedimented organisms which lie with red blood cells at the bottom of the watch-glass. Mix thoroughly in the bulb; seal the capillary tube.

Thread the tubes so prepared on a glass rod bent to three sides of a rectangle, and just able to slide into the upper shelf of an incubator. Keep this incubator at 22° C.

At the end of thirty-six hours, practically every tube shows myriads of single protozoa and large clumps of the parasites in all stages, from those found in the sore to the free flagellar forms.

There are many limits within which I have altered my constituents and temperatures and got positive results, but the above is the most certain and most perfect as yet attained.

The important points to be noted are: (1) The red cells and serum must be heated to 56° C. for five minutes; (2) the medium must be highly acid; (3) the parasites must be freely mixed up with the constituents of the medium ere the red cells deposit with them in the capillary tube; (4) white cells should be avoided as much as possible.

In a successful culture, flagellar forms increase in enormous numbers up to 120 hours, and live symbiotically with masses of cocci and bacilli. Parasites are found in large clusters (flagellates) in 48 hours. In 72 hours pairs of flagellated organisms are frequently found, the one parasite crithidial in shape and staining blue, the other oval or circular and staining rosy-pink; the two organisms are apposed to each other at or about the level of the nucleus of the crithidial form. These pairs are first seen in cultures 48 hours old; the rosy flagellate form then is usually smaller and stains deeper.

DIFFERENTIATION BETWEEN KALA-AZAR AND ORIENTAL SORE

KALA-AZAR

ORIENTAL SORE

FAMILY DISTRIBUTION

An extraordinary tendency to attack a number of persons in the same family or household, this family incidence clearly pointing to house infection.

Rarely, if ever, more than one person attacked.

AGE INCIDENCE

Children most commonly attacked.

Adults the rule.

KALA-AZAR

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RACE INCIDENCE

Immigrants rarely attacked before eight years' residence in the East. The majority of patients seen are natives.

Immigrants attacked within a few months' to a year's residence in the East. The majority of patients seen are natives.

SEASONAL INCIDENCE

No seasonal incidence known, though it is probable that the majority of cases are infected in the cold season.

Affection first appears usually from September to April, and may last for sixteen months and more.

FEVERS TYPICAL OF THE DISEASE

Double remittent type of fever in certain cases. Double continued type. Low continued type. Frequency of different types of fever in various stages of the disease.

No fevers.

RECOVERY AFTER SEPTIC COMPLICATION

Such as cancrum oris.

Septic complications no effect, as the parasite thrives best in cultures with masses of cocci and bacteria.

EFFECT OF QUININE

Large doses in early cases have cured.

No result.

GENERAL SYMPTOMS IN KALA-AZAR

Early cases gave history of rigors daily.

Headache.

None.

Sickness.

None.

Bowels. One-third of cases in hospital show diarrhoea; dysentery in 7 per cent. of such cases.

No bowel trouble.

SPLEEN AND LIVER

Enormous enlargement of both viscera.

None.

Coagulability of the blood decreased.

Increased.

DISTRIBUTION OF THE PARASITE

Polynuclear leucocytes infected.

Superficial polynuclears rarely, if ever, contain the parasites, whereas they swarm in the large mononuclear cells seen in a smear.

Spleen, liver, bone-marrow infected heavily.

Intestinal ulcers and cutaneous ulcers contain the parasite.

CULTIVATION AND DEVELOPMENT OF THE FLAGELLATED STAGE OF THE PARASITE
SHOWING DIFFERENCES BETWEEN THE TWO PARASITES

At 27° C., in blood containing citrate 10 per cent., parasites live for several days and multiply, but there is no material alteration in their form, and no increase in size.

At 28° C., in infected unheated undiluted serum with no citrate, flagellar forms appear in five days.

At 22° C., and not above 25° C., flagellated forms appear.

At 28° C. flagellar forms have been obtained.

Exposure to a temperature of about 25° C. causes rapid death and degeneration of the developing forms.

Sterility of the culture tubes of crucial importance. Contamination with micrococci and bacteria causes rapid death and degeneration of the parasites, staphylococci the most deadly contamination for the parasite.

Contamination with micrococci and certain bacteria highly favourable, as the parasites develop symbiotically with masses of these organisms.

Staphylococci the most favourable contamination. Further, the most perfect monadine forms are seen attached to large masses of staphylococci.

STAGES IN LIFE HISTORY NOTED IN THE PARASITE OF ORIENTAL SORE

(1) Monadine crithidium, very large, and several times the length of a red cell; staining blue, with a scarlet flagellum, carmine extranuclear centrosome, and rosy-violet nucleus.

(2) Flagellated rosy-pink parasite; body oval or circular; apposed to the above at about the level of the nucleus of the monadine crithidium. This presents a small dark-violet staining nucleus, and an extranuclear centrosome staining carmine, from which a long scarlet flagellum arises.

(3) Gregariniform phase of clusters of small parasites, circular, ovoid, or bean-shaped, like enormous cocci. In these the nucleus stains violet. The extranuclear centrosome, when seen, stains red-rosy, and the cytoplasm of the cell pale pink. A few are rose-coloured throughout. These clusters are usually found surrounded by masses of bacteria and cocci staining pale blue.

(4) Early forms of the parasite, showing pyriform, ovoid, and torpedo-shaped elements as ordinarily seen in the infected tissues.

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(5) Larger pyriform cells.

(6) Larger rosy bodies.

The two latter frequently occur in the same group, which may consist of 120 to 200 parasites.

The best method of obtaining clumps of the protozoa from cultures is as follows :—

Blow the contents of the infected tube into a sterile watch-glass gently, then suck up a large drop of red blood deposit; drop this on one end of the slide, and with a fine glass pipette, avoiding actually touching the slide, draw a level film of infected blood serum and citrate to within an inch of the other end of the slide. On removing the glass pipette a large streak of blood mixture remains. Stand the slide on its end against a bottle so that this slowly streams towards the centre of the slide again; when a thickish film is thus made, dry in air and fix in methylic alcohol for five minutes.

The most satisfactory stain for the parasite in all its stages is made up as follows: To 10 c.cm. distilled water add 12 drops of Giemsa solution, shake and pour on the slide, film upwards. Leave to stain for twenty minutes.

At the end of this time the slide will be dark purple. Wash under the tap for thirty seconds, and dip into a watery solution of eosin, 1 in 50,000, for about thirty-five to forty seconds. The film should then seem light rosy-violet. Care must be taken not to stain the film too red.

On examination of a perfectly stained film the torpedo and cockle-shaped forms show up clearly against the faint rose-coloured red cells; the early pyriform and large flagellated monadine forms show up light blue, with scarlet flagella, their nuclei stain purple, their extranuclear centrosomes stain scarlet.

Bacilli and cocci stain deep violet.

The gregariniform phase of the parasite stands out clearly, for these are seen to be four or five times the size of the cocci; their cytoplasm stains rosy-pink, their nuclei violet-blue.

In a later paper Carter¹ draws attention to the various types of Oriental sore which exist in India, mentions a non-ulcerating form, and takes exception to the term Oriental sore. He also refers to the possibility of there being different varieties of *Leishmania* producing these skin lesions. The mention of a non-ulcerating form draws attention to a paper by Thomson and Balfour.² In two cases from Egypt they found curious and multiple growths containing *L. tropica*, coccoid forms, and curious bodies which may or may not have been connected with the specific infection. They suggest the name Leishman nodules for these skin lesions, and enter fully into their histo-pathology. This answered closely to the description given by Jeanselme and Rist in their text-book, and differed in certain respects from the earlier descriptions. They agree with Carter's views above mentioned, and give illustrations of one case and photo-micrographs of sections of the growths, some of which presented the aspect of mountains on a relief map viewed from above. There were frequently secondary growths in the neighbourhood of the main growths with which eventually they coalesced. Leucopenia was present, and the blood from the nodules coagulated rapidly. The second case was apparently infected from the first. Further notes on the parasite and other forms found are given in the Fourth Report of these Laboratories. Culture was only partially successful, flagellated forms not being obtained, but the methods employed scarcely received a fair trial. At the time the paper was written only one instance of a similar condition had been published. As the authors say :—

The exception mentioned is given by Cambillet,³ who recently described the case of a small native boy in Algiers, who presented on the right cheek a tumour, which, to judge from the photograph given, must be almost identical with the face growth in our case. It commenced as a small papule, increased in size until, at the time the paper was written, it measured three centimetres in diameter, and showed no sign of ulceration or discharge. It had persisted for a year in this state. On puncture it yielded blood and *de petits grumeaux blancs*, and in smears *Leishmania tropica* was found. He concluded that the case was one of "Bouton d'Orient," and certainly this term is much more applicable to his case and ours than that of Oriental sore. The latter, in any case, is a misnomer, as instances have been described from Bahia by Juliano Moreira, and recently from Bauru in Brazil by Lindenberg,⁴ who found Leishman bodies present. His work has been confirmed by Carini and Paranhos.⁵

Thomson and Balfour also suggest that the occurrence or non-occurrence of ulceration may depend upon the reaction of the tissue to the virus. If this be strong the epidermic layers thicken; if weak they are destroyed. It may be so, or special forms of *Leishmania* may produce their own specific results; or again, symbiosis with cocci or bacteria may play a part.

¹ Carter, R. M. (November 6, 1909), "A Note on Oriental Sore." *British Medical Journal*.

² Thomson, D. B., and Balfour, A. (1910), "Two Cases of Non-Ulcerating 'Oriental Sore,' better termed Leishman Nodules." *Transactions Society Tropical Medicine and Hygiene*. Also *Journal Royal Army Medical Corps*, January, 1910.

³ Cambillet (July 21, 1909), "Un cas de Bouton d'Orient à Flatters (Alger)." *Bull. Soc. Path. Exot.*

⁴ Lindenberg, A. (May 12, 1909), "L'ulcère de Bauru ou le Bouton d'Orient au Brésil." *Ibid.*

⁵ Carini and Paranhos, U. (May 12, 1909), "Identification de l'ulcère de Bauru avec le Bouton d'Orient." *Ibid.*

Apparently similar growths were soon afterwards described by Ferguson and Richards¹ in Egypt. Bitter and Ferguson had previously found *Leishmania* in ulcerated papillomatous lesions on the limbs of Egyptian fellaheen, and Ferguson and Richards describe that condition, the warty form, more fully, and also a flat, non-ulcerating form. They were unable to differentiate the parasite from the typical *L. tropica*, and state :—

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The examination of a large number of specimens has shown that in those cases in which bacteria were most plentiful, parasites occurred in very scanty numbers or not at all. Our opinion is that, so far from there being anything of the nature of a symbiosis between the two, the appearance of bacteria involves the extinction of the parasite. The reason why we have failed to find the parasites in so many of the cases reported, is probably that this process of extinction had reached a point where exceedingly few, if any, parasites had survived. The specimen which contained the parasite in largest numbers was one which contained no bacteria. Whether the bacteria ever destroy the parasites sufficiently to bring about a natural cessation of the process we have no means of judging, but it seems quite possible.

The result of their researches they summarise as follows :—

- (1) Certain forms of skin affection caused by *Leishmania tropica* occur not infrequently in Egypt.
- (2) They may be solitary or multiple, and in the latter case are almost certainly the result of auto-inoculation.
- (3) They consist essentially of a mononuclear infiltration of the subcutaneous tissues which harbour, sometimes, large numbers of the parasites.
- (4) The lesions manifest themselves clinically under two forms : the one, a slightly raised, smooth, flat patch ; the other, a prominent warty growth. They run a chronic course, and are unaccompanied by constitutional disturbance.
- (5) They are best treated by excision and immediate skin-grafting.

Recently Carter² has again returned to this interesting subject of the non-ulcerating sore, and in a well-illustrated paper states that with our present knowledge we may distinguish three types of Oriental sore : (1) the non-ulcerating Oriental sore ; (2) the superficial flat Oriental ulcer ; (3) the deep-seated Oriental boil. He gives an interesting account of both non-ulcerating and ulcerating forms in natives and Europeans, mentions the Indian names, and states that around Kohat, natives believe the lesions follow the bite of the sand-fly, an opinion which Fink expressed several years ago. Carter says that

the points of interest in the first set of cases as compared with the last are—

- (1) Non-ulcerating character.
- (2) Increased coagulability (of the blood).
- (3) High constant infection of mononuclear cells.
- (4) Rare infection of polynuclears.
- (5) Long history, and appearance of other similar lesions at long intervals.
- (6) Possible infection from another case in close daily contact.
- (7) Primary itching followed by anaesthesia.
- (8) Lesion presents constantly a central smooth surface, papery epithelial scales at periphery, margin indurated and visible to the naked eye.
- (9) Liver and spleen unaffected.
- (10) Possible exacerbations at irregular periods.
- (11) General malaise.
- (12) Occurs at all stages, and in Europeans as well as natives.
- (13) First area affected usually on exposed surface.

He stains smears and films, whether from the patient's tissues or from culture tubes, as previously, stating in addition that

the films should be fixed in methyl alcohol for five minutes and blotted dry before the stain is applied.

The results of his examination of the material obtained from the lesions were very similar to those of Thomson and Balfour. He then enters more minutely than in his first paper into the appearances found in culture, and amongst other notes says :—

A curious feature in cultures of non-ulcerating Oriental sore, first noted by me in October, 1909, is the constant occurrence of enormous clusters of what seem at first sight to be giant cocci. These bodies stain purple, and have often a reddish margin or film round them. They vary from forms the same size as an erythrocyte to smaller forms, altogether like cocci, diplococci, etc. This suspicious and interesting point has since been confirmed by Thomson and Balfour in their work on non-ulcerating Oriental sore in Egypt. In the description of material from an

¹ Ferguson, A. R., and Richards, O. (July 25, 1910), "Parasitic Granuloma; a Condition Allied to Oriental Sore occurring in Egypt." *Annals Tropical Medicine and Parasitology*, Vol. IV., No. 2.

² Carter, R. M. (April 20, 1911), "Non-Ulcerating Oriental Sore, the Cultural Characteristics of the Parasite as compared with a new similar Parasite in *Erthesina fullo* (Thumb.), a Pentatomid Bug." *Ibid*, Vol. V., No. 1.

affected area on the neck, they note, in addition to the parasites found free and in mononuclear cells, groups of what seem to be large cocci, also a number of pale blue homogeneous structureless masses—a condition which is seen to occur also in cultures of the parasite from the intestinal tract of *Erthesina fullo*, to be described later. In material from affected areas on the thigh similar coccoidal bodies were found. These observers describe these blue coccoidal bodies as four to six times the size of the small cocci present. They stain feebly in their centres, often present unstained areas, occur in clumps or pairs, and may resemble huge gonococci.

In the light of recent experiments I am of the belief that the life history of the parasite of non-ulcerating Oriental sore is as follows:—

The cockle-shaped form found in the tissues and mononuclear cells represent the form of the parasite which multiplies in the cells of the host by simple fission. In their earliest form they are seen as an exceedingly minute protoplasmal ring, containing a dot-like nucleus. Such forms are occasionally seen amongst the more maturely developed forms.

After a series of divisions by simple fission in cultures, what would seem to be sexual elements are formed, which stain differently. These seem to pair with interchange of elements. From this point the cycle becomes obscure, and light alone is thrown by observations on the life-cycle of a similar parasite to be subsequently described. If dot-like forms are released from the female cell, as recently seen in *Trypanosoma gambiense*, on examination of infected salivary glands in the intermediate host, the tsetse, these elemental forms might well be the minute bodies occasionally seen in infected mononuclears.

Here then is possibly another rôle for that infective granule which I (A. B.) am convinced will be found to play an important part in many forms of protozoal infection.

Carter then passes on to describe a very similar parasite which he has found in the crop of *Erthesina fullo*, a species of Pentatomid bug common in the Himalayas and in many countries throughout the East. It is a blood-sucker, is attracted by light at night, and enters houses freely. He found the parasite which it harbours has a selective preference for human blood, and while we cannot follow him throughout his interesting description of its life-cycle and the experiments he conducted, the following paragraphs may be quoted:—

To review the points of similarity between the parasite causing non-ulcerating Oriental sore and that infesting the intestinal tract of *Erthesina fullo*.

They both multiply and develop pyriform forms, monadine and circular or oval flagellated forms, in a culture of human blood acidulated with sodium citrate. Neither parasite will develop in an alkaline medium. They both live and develop symbiotically with masses of cocci and bacteria.

Bodies like giant cocci and bluish homogeneous bodies are found in cultures of both parasites.

Pairs of dissimilarly shaped and staining flagellated parasites are seen in both cases, whilst in the parasite of *Erthesina fullo* cyst-like bodies have been found suggestive of the formation of multiple early forms from a fertilised female.

It is probable that these researches will throw fresh light on an interesting and important problem. Hitherto *L. tropica* had only been grown in liquid media or in the liquid portion of solid media, i.e. the blood-stained water of condensation in blood-agar tubes. Nicolle and Manceaux¹ have now succeeded in growing it on the solid part of the modified Novy-MacNeal medium (NNN). They cite two precautions which are necessary if this is to succeed—i.e., do not use an old tube where the surface of the medium is dry; and before inseminating remove the water of condensation with a sterile pipette. One advantage of this method is that much better stained preparations are obtained. These authors² also furnish one of the most important recent papers on the subject, dealing as it does with inoculation and immunisation experiments. It is advisable to give a brief translation of their seventeen conclusions, omitting points already noted in this review:—

- (1) *L. tropica* in Africa Minor is the same as elsewhere, and produces the same kind of lesion.
- (2) The best time for making subcultures appears to be from the tenth to the fifteenth day of the culture. They can be carried on indefinitely.
- (3) In culture *L. tropica* is identical with *L. infantum*. The only apparent difference is that the former is more active.
- (4) The virus is pathogenic for man, the lower monkeys and the dog. With the monkey virus they obtained serial infection in monkeys (three passages) and once with that of man. With the dog virus they obtained serial infection in dogs (three passages).
- (5) The first cultures of *L. tropica*, those made direct from the lesions of human origin, have given the same results in man and monkey.
- (6) In all susceptible animals the lesions are identical. After an incubation period of from 16 to 166 days, usually long and always without any symptoms, hard papular tubercles appear, sometimes tender and involving the skin, which takes on a violet-red hue. The further development varies. They may disappear or pass on to ulceration. Cure results after a longer or shorter period, the longest noted being 90 days. Relapse was observed in two cases.

¹ Nicolle, C., and Manceaux, L. (May 12, 1911), "Culture de *Leishmania tropica* sur milieu solide." *C. R. Soc. Biol.*

² *Idem* (September, 1910), "Recherches sur le Bouton d'Orient." *Ann. de l'Inst. Past.*

- (7) Sections of the lesions show the same appearance as in Oriental sore in man.
- (8) In order to obtain constant positive results with the experimental virus it is necessary to take the material from very young lesions.
- (9) The virus is inactive for the goat, cat, sheep, white rat, horse and ass.
- (10) Strong and repeated doses of culture, if injected into the peritoneal cavity, are deprived of all pathogenic power. In the case of susceptible animals it is therefore necessary to make the inoculation into the thickness of the skin or in its neighbourhood.
- (11) The seat of election for inoculation in the monkey and dog is the nose; for monkeys, the eyelids or their proximity.
- (12) A first attack of Oriental sore confers immunity against a virulent experimental inoculation if the primary lesions are wholly cured and a sufficient time has elapsed. If the second inoculation is practised early during the evolution of the primary lesion, or still more at the time of its appearance, there is, on the contrary, an increased susceptibility shown by a shortening of the incubation period.

The virus of an affected dog can be successfully re-inoculated into the same dog during the evolution of the lesion from which the virus is derived.

(13) A preliminary intraperitoneal inoculation of 100 cultures of *L. tropica* does not confer any immunity on a dog when the animal is afterwards properly inoculated on the skin.

(14) In kala-azar they have demonstrated a negative phase of hyper-sensibility to the virus before the refractory state is established.

(15) A first cured attack of kala-azar protects the dog against inoculation with the virus of Oriental sore. Immunity also exists in this animal against the latter during the whole period of infection with kala-azar.

(16) The strong analogies which exist between the *Leishmania* of Oriental sore and of kala-azar, especially their morphological resemblance and their common pathogenic action for the same three species of animals—man, the monkey, and the dog—in no way indicates that they are one and the same protozoon the degree of virulence of which communicates to the infections of susceptible animals a different character and development. The question can only be settled by a knowledge of the intermediate host which forms the natural reservoir of the virus. If it is shown that the same vector is operative in both cases one may conclude that the *Leishmania* are not identical. If, on the contrary, there are two different vectors, it will suffice to infect each of them with the ordinary virus of the other, and a conclusion can then easily be drawn according as the effects on the same vector with the two viruses are or are not identical.

It is already known that the virus of kala-azar introduced into the neighbourhood of the skin in susceptible animals does not produce lesions identical with those of Oriental sore.

(17) There is reason to suspect the dog as a natural reservoir of the virus of Oriental sore. If so, this animal plays a very important rôle in the etiology of *Leishmania* infections.

In a still later paper Nicolle and Manceaux¹ present some new facts, the result of further work. They describe a curious case wherein a man inoculated with *L. tropica* from a monkey strain showed an incubation period of seven months. They think this may be due to the fact that the appearance of the lesion followed closely on an attack of Malta fever, and that the latter had diminished the resistance to the parasites and permitted such as survived to develop.

Sections of organs of infected dogs show no parasites. Observations on dog and man seem to indicate that a first non-effective inoculation of the virus or culture confers resistance to the inoculation of an active virus in the latter. The immunity conferred by a first successful experimental inoculation, however, does not appear very stable or very durable.

The result of Wenyon's² recent investigations in Bagdad has been issued in the form of a report. A good deal of interesting work has been accomplished, but nothing very special has been elicited. The research was conducted with a view to clearing up the following points:—

- (1) The characters and course of the disease in man.
- (2) The examination of lower animals for signs of the disease and inoculation of these from man.
- (3) Study of the various biting flies, ticks, etc., found in Bagdad.
- (4) Experiments with the biting flies fed on date boil cases and dissection of flies.
- (5) Examination of the date boil parasite as it occurs in the sore.
- (6) Culture experiments with the date boil parasite.

As regards (1) Wenyon notes that the terms male and female sore are justified clinically. As the types of two extremes there exist the ulcerating and the non-ulcerating sores. The former is the so-called female sore, the latter the male. He describes their appearance, and indicates that the incubation period, about which it was difficult to obtain precise information,

¹ Nicolle, C., and Manceaux, L. (March 8, 1911), "Données expérimentales nouvelles sur le Bouton d'Orient." *Bull. Soc. Path. Exot.*

² Wenyon, C. M. (April 1, 1911), "Report of Six Months Work of the Expedition to Bagdad on the Subject of Oriental Sore." *Journal Tropical Medicine and Hygiene.*

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continued

may be as short as a fortnight. The disease usually lasts a year, and the male sore may never break down. In the ulcerating type he found streptococci, staphylococci, various bacilli, and frequently a diplococcus resembling very closely the gonococcus, in that it occurs in pairs within the pus cells. He mentions a subacute ulcer liable to be confounded with the true date boil in which this organism is present. One attack, provided the sore is completely healed, confers permanent immunity, but Wenyon records one fact which, in the light of the view held by Markham Carter, Thomson, and myself, may prove significant, namely, that persons who have suffered from Aleppo boil, coming to Bagdad, have been known to contract the Bagdad lesion.

The parasite was not found in the peripheral blood, and there are no constitutional symptoms.

As regards (2) the author states that dogs are supposed to suffer from date boil about the nose. He examined a few such sores, but failed to find *L. tropica* in them, nor did he find this parasite in a dog with an ulcerating condition of the legs which had been regarded as date boil even after repeated examinations. He examined cats and rats with a negative result, and inoculated rats, rabbits, birds, and even ticks, in vain. Camels are rare in Bagdad. There was no evidence that the horse, mule, donkey, or ox had anything to do with the disease. With respect to (3 and 4) Wenyon passes in review the possible rôle of house-flies, *Stomoxys*, *Hippoboscidae*, *Tabanidae* (not found in the town). Fleas, lice, ticks, bed-bugs, sand-flies (*Phlebotomus*), and mosquitoes. He finds that house-flies can readily take up the virus, and can undoubtedly act as mechanical vectors, carrying the parasite to a wound or sore, but he is unable to throw any further fresh light on the subject, save that he found a partial development of *L. tropica* in the bed-bug, due, he thinks, merely to the favouring influence of the large amount of blood ingested by this insect. Under (5) he describes the parasite in the sore, noting that forms without nuclei are frequently seen. He regards them as probably degeneration forms. Re (6), culture was successful. Rabbit blood-agar is a better medium than that prepared with dog's blood. It is unfortunate that Wenyon could not obtain animals susceptible to inoculation. Had he been able to work with monkeys he might have confirmed and extended the researches of Nicolle and Manceaux. The examination of the peripheral blood has been mentioned. The only observer who has found *L. tropica* in this situation is Neumann.¹ On two occasions, with six months interval between them, he has seen parasites free in the plasma of blood taken from the finger, and states that at these times the patient suffered from a feeling of fatigue and from a slight access of fever.²

Billet² has described a case of Biskra bouton. Like others, he found that blood from the congested zone at the periphery of the lesion showed an increase of mononuclears which was not present in finger blood. Commenting on the case, Jeanselme pointed out that certain forms of Oriental sore resembled warty and vegetative tuberculous skin lesions, *i.e.* some varieties of lupus.

Gros,³ who has published an account of four cases on the Algerian littoral, is of Carter's opinion as regards direct transmission from case to case. In no instance was infection transmitted from his cases to those in contact with them. How close this contact is likely to have been any one conversant with North African customs and usages knows. Gros concludes that "le bouton d'Orient paraît donc peu contagieux."

Row⁴ has described the changes the flagellate body undergoes in cultures *in vitro*. Coccid bodies appear amongst the disintegrating masses of flagellates, and the condition seems to be something like that described by Carter. He stated that—

Compared with Nicolle's result, it would appear that the Tunisian (Nicolle's) parasite is distinct from the Indian species. Experiments on monkeys—*Macacus sinicus*—showed that after the contents of a sore from the human lesion were used to infect a monkey by cutaneous scarification, tiny nodules formed at the seat of the lesion, and in the fluid obtained parasites of a larger type than in the human lesion were found. This would seem as if the parasite had undergone the first stage of development. Further cultures and experiments with monkeys appeared to demonstrate that the sore in monkeys is distinct from Nicolle's observations in Tunis. There seems no proof that a biting insect is required for the production of the disease, but rather that the common house-fly is the transmitting agent. Patients with Oriental sores are often seen with swarms of flies around them, and it

¹ Neumann, R. O. (1909), "*Leishmania tropica* im peripheren Blute bei der Dehlibeule." *Cent. f. Bakt., I. Orig.*, Vol. LII.

² Billet, A. (February 10, 1909), "Sur un cas de Clou de Biskra (avec présentation du malade)." *Bull. Soc. Path. Exot.*

³ Gros, H. (June 9, 1909), "L'ulcère à *Leishmania* (Bouton d'Orient) sur le littoral algérien." *Bull. Soc. Path. Exot.*

⁴ Row, R. (August 1, 1910), "Further Observations on *Leishmania tropica* of Oriental Sore of Cambay, India." *Journal Tropical Medicine and Hygiene.*

is not unlikely that the parasites from their sores could be transferred directly from person to person, either in the legs of the fly or through its excreta, and an accidental nail scratch, made owing to the tickling of the fly on the spot, would be all that is necessary for the infection.

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continued

Darling¹ has recorded a case of autochthonous Oriental sore from Panama, a new locality. One may say here that it has also been found in French Guiana, New Caledonia, and the region of the Zinder in Africa, where it forms one type of craw-craw. In Darling's case the histo-pathology of the ulcer was not unlike in certain particulars that of the Leishman nodules (*loc. cit.*). The author suggests Dermal Leishmaniasis or Ulcerating Leishmaniasis as a name for the condition, but, as already stated, Superficial Leishmaniasis would be better, for some cases show no ulceration, and quite recently Carini² has described and illustrated a case of Leishmania of the rhino-buccal-pharyngeal mucosa, occurring in Brazil. The disease began with ulcers of the legs, but a year after their appearance an erosion of the palate commenced. The disease followed a slow and painless course, eventually involving the nose and pharynx. Typical *L. tropica* were found in the lesions. Carini says that infections of the mucosa occur almost always in patients who have been suffering from the cutaneous form. Sometimes it is merely a question of spread from the skin to the neighbouring mucous membrane, but in other cases the lesion starts *de novo* in the latter, as, for example, the palate, and in such cases the condition is not likely to be due to auto-inoculation from the skin lesions. He believes mucous membrane infections are more common than is thought to be the case, and points out that the absence of giant cells in the lesions is important in distinguishing Leishmaniasis from blastomycosis. In the latter, giant cells, as a rule, are very numerous.

The natural immunity of mice to inoculations with cultures of *L. tropica* has been the subject of study by Delanoe,³ but we can only give the reference and hurry on to the subject of treatment, about which there is little to be said, although recent work has made the outlook more hopeful.

Marzinowsky's method was mentioned in the First Review. Billet (*loc. cit.*) cites the plan adopted by Benoit, namely, (1) Cleanse the surface thoroughly and then dust it with finely powdered permanganate of potash. (2) At the end of 8 or 10 days, after removing the crust which has formed, paint the brawny elevations with a 1 in 10 solution of methylene blue. This method has been successfully used in twenty-one cases of the North African type. Bussière and Nattan-Larrier⁴ mention the use of iodine, silver nitrate, carbolic acid, permanganate of potash and methylene blue, but think that in many cases excision is indicated. With this finding Laveran does not agree, believing it to be contra-indicated in all cases, and possibly also dangerous. References are given to methods described by Gueytat and Moty.⁵ Avisa⁶ mentions Lincoln's treatment as used in India. It consists in the application of "rausath," a dark green fluid prepared from a very dark green gummy exudation, dried in and mixed with the leaves of the tree from which it is obtained. This is painted over the sore and allowed to dry, no dressing being applied. Every day a fresh coat is painted over the old one. A scab comes away after about a fortnight, and the surface is found completely healed. This method deserves to be widely known, and should be fully tested.

Benoit-Gonin⁷ gives more details regarding the permanganate treatment, which, it is maintained, leaves no brown pigmentation in the scar; but of greater interest is a paper by Nicolle and Manceaux⁸ on the use of salvarsan in two cases, one multiple. They gave the drug by intramuscular injection. In the first and milder case the dose of 0.3 gramme was not sufficient, and the benefit was temporary; in the second case 0.6 gramme was given, the result being remarkable, the condition being nearly cured in five days, and wholly so in twenty. An interesting and recent development is the employment by Broome⁹ of carbonic acid snow.

¹ Darling, S. T. (December, 1910), "Autochthonous Oriental Sore in Panama." *Transactions Society Tropical Medicine and Hygiene*.

² Carini, A. (May 10, 1911), "Leishmaniose de la muqueuse rhino-bucco-pharyngée." *Bull. Soc. Path. Exot.*

³ Delanoe, P. (March 17, 1911), "L'immunité naturelle de la souris à l'égard des cultures de Kala-azar et de Bouton d'Orient Tunisiens." *C. R. Soc. Biol.*

⁴ Bussière, A., and Nattan-Larrier, L. (June 9, 1909), "Essais de Traitement du Bouton d'Orient." *Bull. Soc. Path. Exot.*

⁵ Gueytat and Moty (November 10, 1909), "Note sur le Traitement du Clou de Biskra." *Ibid.*

⁶ Avisa, W. G. (July, 1910), "The Treatment of Oriental Sore." *Journal Royal Army Medical Corps*.

⁷ Benoit-Gonin (April 12, 1911), "Note sur le Traitement du Bouton d'Orient." *Bull. Soc. Path. Exot.*

⁸ Nicolle, C., and Manceaux, L. (April 12, 1911) "Application de L'arsénobenzol au Traitement du Bouton d'Orient." *Ibid.*

⁹ Broome, H. H. (April, 1911), "The Treatment of Oriental Sore." *Indian Medical Gazette*.

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continued It is applied with firm pressure for forty seconds to thick and dense portions, and twenty-five seconds to the edges. There is some burning pain at the time of application, which rapidly passes off, to be followed during the reaction stage by a more severe and prolonged burning sensation. A blister forms which may be punctured. Cotton wool is applied and healing takes place under a scab. A small sore will apparently heal up in ten days. There certainly seems a future for this simple and effective method.

Parasites. It is quite impossible in a review of this nature to deal with all the papers relating to the subject of parasites, and although it is somewhat difficult to draw any hard and fast line as to the papers that should be included, it is hoped that the references given will be found useful to the worker in the Tropics. As in the last Review, the article is limited almost wholly to the metazoa. Some grouping has been attempted but it is not easy to classify so many aspects of a large subject.

The rôle played by parasites in causing disease either directly or indirectly was considered in our first Review and scarcely requires further mention, but one may quote some remarks by Washburn¹ in a paper dealing with "Health in the Philippines."

There appears to be a greater abatement among civilians than among soldiers of diseases due to intestinal parasites. Intestinal diseases due to parasites are positively known to be preventable by the exercise of sufficient care in eating and drinking. Fortunately, too, the great majority of cases yield to treatment. There is reason to believe that in the near future intestinal parasites, through the achievements of preventive medicine, may cease to be important factors in producing intestinal diseases. This accomplishment will be almost as much of a boon to the tropics as was the discovery of the means of preventing yellow fever.

In a note in the *Lancet* reference is made to a series of papers published by Stiles and Goldberger² relating to parasitic worms.

A peculiar case of parasitism in man was observed in Florida :—

The worms, which live in the subcutaneous tissue and cause swelling resembling acne, have been determined as very closely related to, and perhaps identical with, *Sparganum proliferum*. This parasite has been reported on only one former occasion, when it was found in Japan, but its life history, source of infection, prevention, and treatment are still unknown. Its chief peculiarity is a reproduction in its larval stage by the formation of supernumerary heads, which may become independent and wander through the tissue.

Shipley³ has an interesting paper entitled "A Cause of Appendicitis and other Intestinal Lesions in Man and other Vertebrates." The paper is too long to be fully referred to, but one notes that mention is made of the important part played by parasites as a cause of appendicitis. Shipley mentions in particular *Oxyuris vermicularis*, *Ascaris lumbricoides*, and *Trichocephalus trichiurus*, and gives various references to papers illustrating the part played by these nematodes in the causation of appendicitis and peritonitis.

The same author⁴ has an interesting paper referring to the relation of certain cestode and nematode parasites to bacterial disease. In this paper a description is given of a fatal epidemic disease among rainbow trout caused by nematode worms, some of which had penetrated to the swim bladder of the fish, apparently from the intestine, through the intervening tissues. The swim bladder of infected fish showed extensive invasion by intestinal bacteria, while the same organ in healthy fish was entirely free from such organisms. Allusion is also made to the occurrence of a species of *Strongylus quadriradiatus* in the intestines of pigeons which had died from an unknown malady. The intestinal walls of the pigeons were in all probability pierced by the parasite, and thus permitted the passage of the bacteria from the interior of the bowel into the peritoneal cavity.

Manson and Sambon⁵ describe a case of intestinal pseudo-parasitism due to *Chilodon uncinatus*, a ciliated infusorian. The patient infected with this parasite complained only of slight looseness of the bowels for several years. As *Chilodon uncinatus* is, as a rule, a free living organism inhabiting fresh-water bodies, its presence in the intestine of man must be looked upon rather in the light of a chance or pseudo-parasite.

Rather a useful paper by Royal⁶ refers to the subject of pseudo-parasites, and will be

¹ Washburn, W. S. (September, 1908), "Health Conditions in the Philippines." *Philippine Journal of Science*, B.

² Stiles, C. W., and Goldberger, J. (1908). *United States Public Health and Marine Hospital Service, Washington, Bulletin* No. 40. Quoted in *Lancet*, July 11, 1908.

³ Shipley, A. E. (December, 1908), "A Cause of Appendicitis and other Intestinal Lesions in Man and other Vertebrates." *Parasitology*.

⁴ *Idem* (1909), "On the Relationship of certain Cestode and Nematode Parasites to Bacterial Disease." *Journal of Economic Biology*.

⁵ Manson, P., and Sambon, L. W. (March 20, 1909), "A Case of Intestinal Pseudo-Parasitism due to *Chilodon uncinatus* (Blochmann)." *Lancet*.

⁶ Royal, M. A. (March, 1908), "Pseudo-Parasites." *Bulletin of the State University of Iowa*, No. 182.



